



The Golden Grapes of Wrath — *Staphylococcus aureus* Bacteremia: A Clinical Review

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ABSTRACT

Staphylococcus aureus bacteremia is common and associated with fatality rates approximating 25%. We provide a brief overview of *S. aureus* bacteremia from a clinical and microbiological lens and review the relevant evidence and literature gaps in its management. Using a case-based approach, evidence and clinical judgement are meshed to highlight and justify the 5 core interventions that ought to be performed for all cases of *S. aureus* bacteremia: 1) appropriate anti-staphylococcal therapy, 2) screening echocardiography, 3) assessment for metastatic phenomena and source control, 4) decision on duration of antimicrobial therapy, and 5) Infectious Diseases consultation.

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CLINICAL CASES

Case 1

A 78-year-old woman is hospitalized with hypoxemia. Index blood cultures (BCx) did not isolate a pathogen. A diagnosis of congestive heart failure was made and she improved with diuresis. Four days later she developed swelling and tenderness at her peripheral intravenous line site. BCx yielded methicillin-sensitive *Staphylococcus aureus* (MSSA) and her intravenous line was removed. There are no other sites of infection and repeat BCx taken 2 days after antibiotic initiation are negative.

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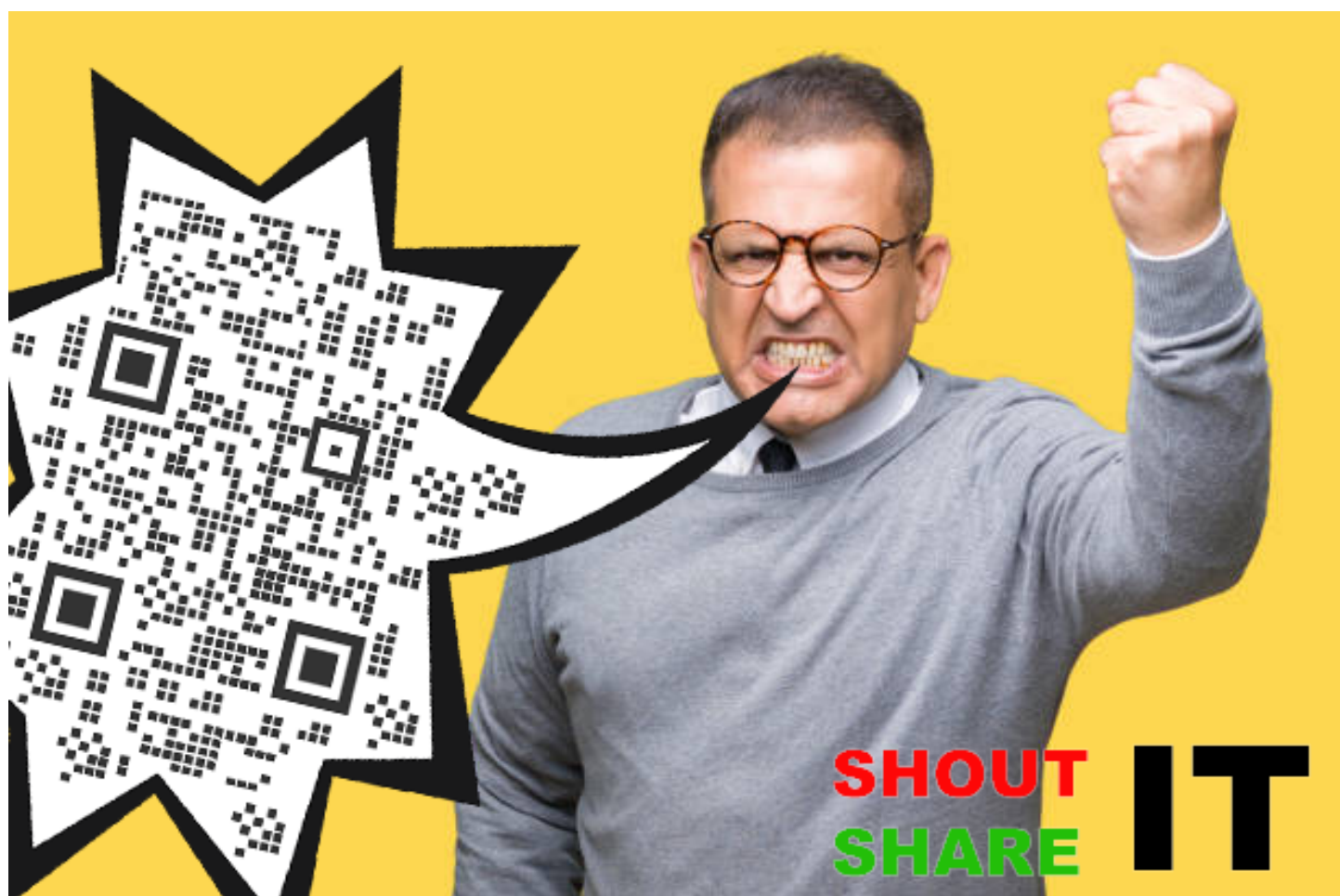
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Case 2

A 45-year-old man with lumbar degenerative disc disease presents with a 2-day history of low back pain after sustaining a musculoskeletal injury from lifting furniture 1 week ago. Accompanied by fevers and chills, his examination is relevant for L5 vertebral tenderness. BCx are positive for MSSA. Plain radiographs and magnetic resonance imaging (MRI) of his lumbar spine are unremarkable.

Case 3

A 29-year-old woman who injects drugs is hospitalized for left knee pain and methicillin-resistant *S. aureus* (MRSA) bacteremia. Clinical assessment reveals a tender, swollen joint with limited range of motion. Synovial fluid culture from an irrigation and debridement of her left knee yields MRSA. A transthoracic echocardiogram (TTE) reveals a 0.5 cm × 0.5 cm vegetation on her tricuspid valve with moderate tricuspid regurgitation. Despite 8 days of therapeutic vancomycin, serial BCx remain positive for MRSA. Computed tomography (CT) of her chest, abdomen, and pelvis is unremarkable.



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Questions to consider for each patient:

1. What other investigations should be considered?
2. What is the role of echocardiogram?
3. What choice, route, and duration of antibiotic(s) should be administered?
4. What is the role of Infectious Diseases (ID) consultation?

EPIDEMIOLOGY AND RELEVANCE

S. aureus is a colonizer of mucous membranes, skin, and gastrointestinal tract, carried by up to 80% of the population. Nasal carriage of *S. aureus* is most common, and increases with health care exposure, diabetes, dialysis, substance drug use, and human immunodeficiency virus infection.¹ While most carriers of *S. aureus* do not go on to develop illness, colonization often precedes infection.

S. aureus bacteremia remains a common cause of bloodstream infection. It has an annual population-based incidence rate upwards of 50 cases/100,000 population and mortality rate approximating 20%-30% in developed countries despite effective antibacterial therapies and source control strategies.² In contrast, 30-day mortality from an acute myocardial infarction approximates 10%.³

In the United States, prevalence of MRSA amongst *S. aureus* clinical isolates is upwards of 50% and significant enough to justify empiric MRSA treatment in *S. aureus* bacteremia. However, rates continue to decrease with rigorous infection control measure implementations.⁴ In comparison, both Canada and Europe have lower MRSA prevalence, although European MRSA prevalence increases substantially with decreasing latitude (eg, <5% in Northern European countries compared with over 25% among Southern Europe).⁵

Patients with *S. aureus* bacteremia have a spectrum of clinical presentations; some are asymptomatic with incidentally identified primary bacteremia, while others have a sustained bloodstream infection complicated by embolic phenomena. The mechanism of disease from *S. aureus* is not well understood and thought to be mediated by the relationship between host susceptibility and pathogen virulence factors.

Despite the lethality of *S. aureus* bacteremia, there remain no contemporary uniform guidelines to inform clinical practice. Rather, the evidence that guides the treatment of patients with *S. aureus* bacteremia focus on specific questions (eg, comparison of antibacterials,

comparison of cardiac imaging modalities) rather than *S. aureus* bacteremia as an entity in itself.^{6,7} Regardless, a series of diagnostic and therapeutic investigations should be performed in all patients with *S. aureus* bacteremia. These include: 1) appropriate anti-staphylococcal therapy, 2) screening echocardiography, 3) assessment for metastatic phenomena and source control, 4) decision on duration of antimicrobial therapy, and 5) ID consultation (Figure).

CLINICAL SIGNIFICANCE

- *Staphylococcus aureus* is responsible for a diverse burden of human diseases.
- *S. aureus* bacteremia is common, and has fatality rates approximating 25%.
- *S. aureus*' affinity for foreign material and antimicrobial resistance renders *S. aureus* bacteremia treatment challenging.
- In patients with *S. aureus* bacteremia, the following interventions should be undertaken: 1) appropriate anti-staphylococcal therapy, 2) screening echocardiography, 3) assessment for metastatic phenomena and source control, 4) decision on duration of antimicrobial therapy, 5) Infectious Diseases consultation.

MICROBIOLOGY

S. aureus is a Gram-positive, facultatively anaerobic coccus with unique virulent properties. In brief, *S. aureus* adhesins allow migration into the bloodstream followed by attachment to biotic and abiotic surfaces. Once attached, *S. aureus* coagulase interacts with fibrinogen to form hardy, drug-resistant biofilms.⁸

Toxins produced by *S. aureus* can lyse leukocytes and evade host immune systems. Certain *S. aureus* strains, particularly within community-acquired MRSA, produce Panton-Valentine leukocidin (PVL), a cytolytic toxin associated with granulocyte destruction. The presence of PVL can be associated with severe, deep-seated *S. aureus* infections in hosts with high inflammatory markers but relative leukopenia.⁹ While in vitro data of *S. aureus* strains with PVL suggests a benefit with usage of adjunctive toxin inhibitory antibiotics such as rifampin, clindamycin, or linezolid, clinical benefit has not been reflective of the same.¹⁰

S. aureus is seldom considered nonpathogenic when identified in BCx. Risk factors associated with *S. aureus* contamination are not well defined. In our experience, pseudobacteremia is more common among patients with papulosquamous skin disease (eg, eczema, psoriasis). If contamination is suspected, close follow-up with clinical monitoring and serial BCx is advised.

Time to BCx positivity may predict speciation, severity, and etiology of staphylococcal bacteremia. For example, 1/4 positive BCx for Gram-positive cocci in clumps after 24 hours are more likely to be coagulase-negative *Staphylococci*, whereas *S. aureus* BCx positivity within 14 hours is associated with endovascular infection, persistent bacteremia, and metastatic complications.¹¹ Time to positivity difference of ≥ 2 hours between BCx taken from central lines and those taken from peripheral sites are suggestive of central-line-associated bloodstream infection.

Bacteremia with MRSA is associated with poorer clinical outcomes compared with MSSA; likely due to increased

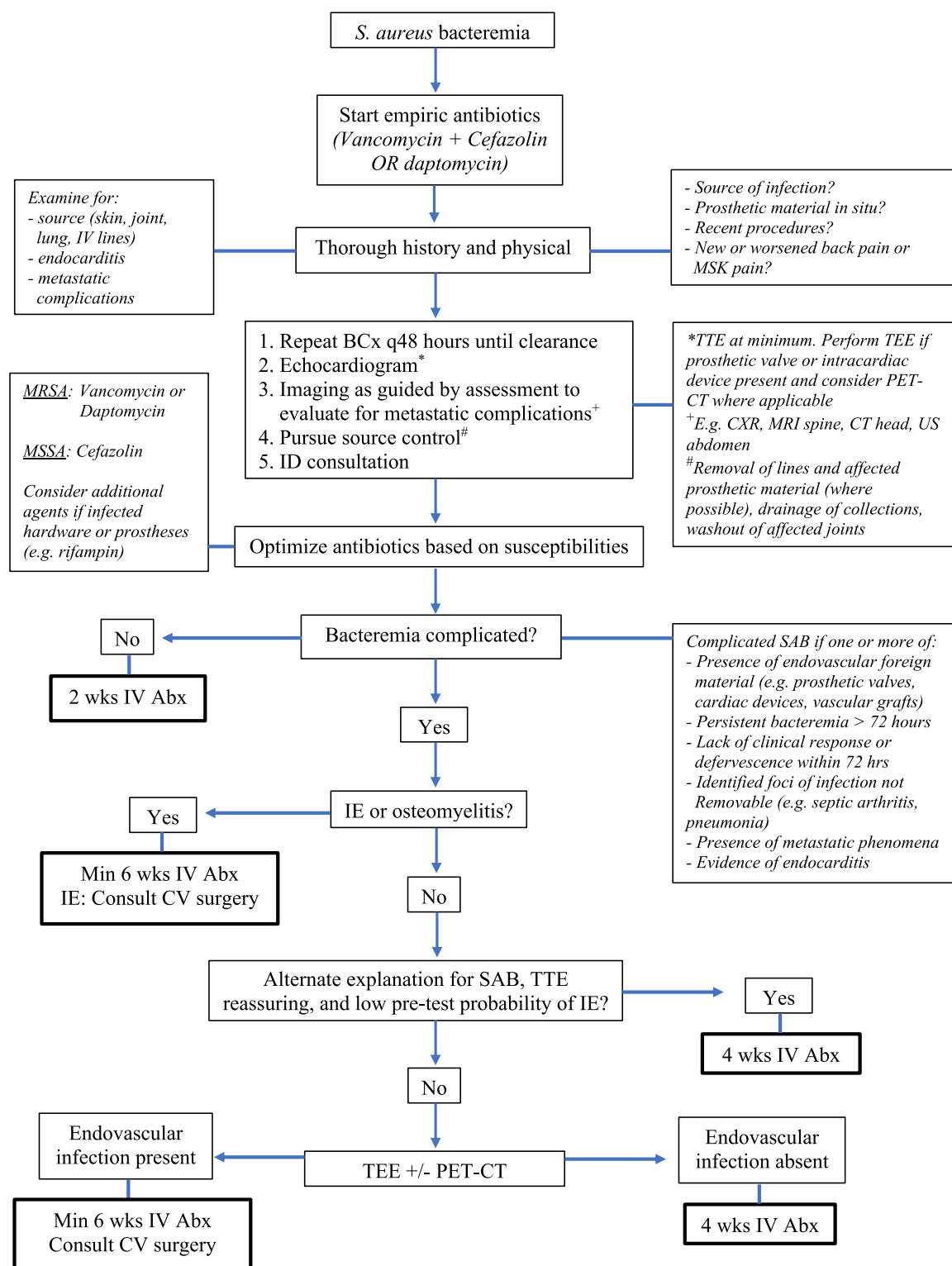


Figure Proposed flow diagram for *Staphylococcus aureus* bacteremia management. May differ depending on recommendations by local ID consultants.

Abx = antibiotic; BCx = blood culture; CT = computed tomography; CV = cardiovascular; ID = Infectious Diseases; CXR = chest X-ray study; IE = infective endocarditis; IV = intravenous; MRI = magnetic resonance imaging; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; PET-CT = positive emission tomography-computed tomography; SAB = *S.aureus* bacteremia; TEE = transthoracic echocardiogram; TTE = transthoracic echocardiogram.

virulence and drug-resistance. The dysfunction of the accessory gene regulator (*agr*), a protein that modulates *S. aureus* virulence factors, is a key contributor to virulence of MRSA. Its dysfunction is associated with prolonged bacteremia via increasing glycopeptide (e.g. vancomycin) resistance through various mechanisms including adhesin overexpression.¹²

Antimicrobial resistance to vancomycin in *S. aureus* can develop in 3 main ways: modifications of *S. aureus*' cell wall, "minimal inhibitory concentration (MIC) creep," and acquisition of *vanA* plasmids.

Vancomycin (or glycopeptide)-intermediate *S. aureus* (VISA or GISA) and heterogenous VISA (hVISA) strains are less susceptible to vancomycin due to increasing cell wall thickness. Compared with VISA, the number of *S. aureus* subpopulations in hVISA have variable ranges of vancomycin susceptibility. In contrast, MIC creep is not a method of resistance per se but represents a phenomenon of increasing vancomycin MICs among *S. aureus* over time. Compared with an MIC <2 ug/mL, isolates of MRSA with a MIC of 2 ug/mL treated with vancomycin may be associated with unfavorable clinical outcomes and be precursors to VISA and hVISA.¹³ However, interpretation of vancomycin "MIC creep" and its clinical relevance remains varied. Both the American and European susceptibility guidelines continue to recommend MRSA isolates with a MIC of 2 ug/mL susceptible to vancomycin, although some centers may report caution with vancomycin use in these cases. Vancomycin MICs between 4 and 8 ug/mL (VISA, hVISA) and MIC $\geq$ 16 ug/mL (VRSA) are reported as indeterminate and resistant, respectively. Vancomycin resistance is rare and most commonly mediated by acquisition of *vanA* plasmids from vancomycin resistant *Enterococci*. *VanA* confers resistance by altering the peptide target of glycopeptides.

Even less common is resistance to daptomycin, tigecycline, linezolid, and anti-MRSA beta-lactams (ceftobiprole, ceftaroline) among *S. aureus* strains. Increasing MICs to vancomycin and daptomycin appears to decrease the MICs for anti-MRSA beta-lactams and is referred to as the "see-saw effect." It is thought that the beta-lactam decreases cell membrane positive charge, thereby enhancing daptomycin binding.¹⁴ Clinical studies examining the combination of beta-lactams with vancomycin or daptomycin have shown improved time to MRSA blood clearance but increased rates of acute kidney injury.¹⁵

APPROPRIATE ANTI-STAPHYLOCOCCAL THERAPY

Empiric *S. aureus* Bacteremia Therapy

Empiric antibiotic selection in *S. aureus* bacteremia is critical. Vancomycin monotherapy in MSSA bacteremia is associated with worse clinical outcomes compared with anti-staphylococcal beta-lactams.¹⁶ When susceptibilities of *S. aureus* bacteremia are not yet known, patients with *S. aureus* bacteremia should be treated with combined anti-

staphylococcal beta-lactam and anti-MRSA agent. De-escalation and appropriate monitoring should be performed once susceptibilities are known.

MSSA Bacteremia

Anti-staphylococcal penicillin or cefazolin are preferred and clinically superior to broad-spectrum antibiotics with anti-staphylococcal coverage in MSSA bacteremia. While piperacillin/tazobactam and non-first-generation cephalosporins have activity against MSSA, their use in MSSA bacteremia is associated with higher mortality and worse outcomes.¹⁷ Some exceptions may include febrile neutropenia with mixed infections where broad spectrum anti-staphylococals may be favored over combination beta-lactam therapy.¹⁸ In patients with *S. aureus* bacteremia who require additional Gram-negative or anaerobic therapy, we recommend discussion with ID to optimize the patient's antimicrobial regimen without sacrificing ideal anti-staphylococcal coverage.

We recommend cefazolin as first-line therapy for MSSA bacteremia. Anti-staphylococcal penicillins have similar efficacy to cefazolin but are associated with higher rates of adverse events, including interstitial nephritis.¹⁹ It was traditionally believed that anti-staphylococcal penicillins were superior for penetration of the central nervous system compared with cefazolin, but a growing body of pharmacokinetic studies is reassessing this dogma—and highlighting that cefazolin is a viable option in treating MSSA bacteremia with central nervous system involvement.²⁰

MRSA Bacteremia

Intravenous vancomycin or daptomycin are appropriate for MRSA bacteremia, depending on the clinical scenario. Vancomycin is challenging to dose, as reaching therapeutic levels and steady state depends on a host's volume of distribution and renal function. Traditionally, vancomycin trough concentrations of 15-20 mg/L were thought to achieve sufficient serum vancomycin concentrations to eradicate MRSA. However, contemporary guidelines recommend targeting an area under the curve (AUC) over 24 hours to MIC (AUC/MIC) between 400 and 600 mg/h/L (assuming a vancomycin MIC of 1 mg/L) to minimize vancomycin toxicity.²¹ Compared with monitoring vancomycin trough concentrations, AUC-guided therapeutic drug monitoring is labor intensive and requires additional time-critical phlebotomies. Accordingly, some institutions recommend monitoring vancomycin levels to achieve a less restrictive trough concentration of 10-20 mg/L as an alternate strategy to balance drug efficacy against drug toxicity in settings that lack the resources to do AUC-guided monitoring.²²

The increasingly recognized limitations of vancomycin have prompted usage of daptomycin as an anti-staphylococcal for MRSA bacteremia. Daptomycin is a lipopeptide antibiotic that inserts and disrupts the integrity of the staphylococcal cell wall, leading to rapid depolarization and bacterial cell death. Initial studies demonstrated noninferiority

Table 1 Anti-Staphylococcal Drugs for *Staphylococcus aureus* Bacteremia

	Common or Severe Adverse Reactions	Regular Monitoring (weekly)	Considerations
Cefazolin*	Acute interstitial nephritis [†]	CBC-diff, Cr	Hypersensitivity cross-reaction of cefazolin with other beta-lactams is rare. Consider its use even in people with documented non-anaphylactic allergy to penicillins or other cephalosporins.
Cloxacillin, nafcillin, oxacillin	Hematologic dyscrasias Rash [†] Hypersensitivity including anaphylaxis [‡]		Cloxacillin, nafcillin, oxacillin • No renal adjustment needed • Generally requires central line access due to issues with skin irritation and risk of thrombophlebitis when using a peripheral catheter
Vancomycin	Nephrotoxicity Neutropenia Thrombocytopenia DRESS	CBC-diff, Cr, pre-vancomycin level [‡]	Infusion reaction: resolve by decreasing rate of infusion
Daptomycin	Myositis [§] Eosinophilic pneumonia	CBC-diff, Cr, CK	Inhibited by pulmonary surfactant; recommend against usage in pulmonic infections
Linezolid	Myelosuppression with ≥ 2 weeks of use Lactic acidosis Drug interactions	CBC-diff	No renal adjustment needed Excellent pulmonic tissue penetration Not recommended as first-line therapy in <i>S. aureus</i> bacteremia

CBC-diff = complete blood count and differential; CK = creatine kinase; Cr = creatinine; DRESS = drug rash with eosinophilia and systemic symptoms.

*Consider higher dosing for elevated body mass index (3 g IV every 8 hours) in adults over 100 kg in weight, assuming a normal creatinine clearance.

[†]More common with anti-staphylococcal penicillins than cefazolin.

[‡]Target area under the curve/minimal inhibitory concentration (MIC) of 400-600 mg/h/L (assuming a vancomycin MIC of 1 ug/mL). Alternatively, monitor vancomycin levels to achieve trough concentration of 10-20 mg/L.

[§]Suspend statin while on daptomycin therapy.

^{||}Risk of serotonin syndrome with concomitant selective serotonin reuptake inhibitors, risk of severe hypertension with concomitant monoamine oxidase inhibitor.

when comparing daptomycin with vancomycin in MRSA bacteremia.²³ Daptomycin is an acceptable agent for MRSA bacteremia and may confer advantages over vancomycin in isolates with an MIC ≥ 2 .

Linezolid is an oxazolidinone, a bacteriostatic protein synthesis inhibitor with enhanced in vitro activity in MRSA toxin-producing isolates. While linezolid is reliably utilized for MRSA meningitis, skin and soft tissue infection, and pneumonia, usage in bacteremia has been associated with higher mortality when compared with daptomycin or vancomycin.²⁴ Thus, daptomycin and vancomycin remain preferred agents in MRSA bacteremia.

Monitoring parameters and considerations of anti-staphylococcal agents are summarized in Table 1.

New Developments

Ceftaroline and ceftobiprole are fifth-generation cephalosporins with in vitro activity against MRSA and approved for treatment of skin and soft tissue infection and community-acquired pneumonia.^{14,25} Smaller studies have demonstrated promise in usage for MRSA bacteremia, particularly when clinical failure is observed with intravenous vancomycin or daptomycin. In cases of persistent bacteremia despite appropriate therapy, we recommend ID and

Microbiologist consultation if ceftaroline or ceftobiprole usage is being considered due to clinical failure.

Discussions on usage of oral anti-staphylococcal agents have become more robust over the last few years. A significant body of literature exists for usage of linezolid in select cases of *S. aureus* bacteremia given its excellent oral bioavailability.²⁶ While usage of fluoroquinolone with rifampin was found to have equal efficacy to vancomycin in select cases of right-sided infective endocarditis (IE), its applicability to other cases of *S. aureus* bacteremia remains questionable. Usage of trimethoprim-sulfamethoxazole, tetracyclines, clindamycin, and oral beta-lactams are not advised owing to a lack of evidence.²⁶ Based on available evidence, we recommend usage of linezolid or fluoroquinolone and rifampin only as salvage therapy when other options are not possible (eg, patients prematurely discharged from hospital with *S. aureus* bacteremia).

SCREENING ECHOCARDIOGRAPHY AND CARDIAC IMAGING

Echocardiography in patients with *S. aureus* bacteremia is supported by the European Society of Cardiology and the Infectious Diseases Society of America.^{27,28} Upwards of 18% of individuals with *S. aureus* bacteremia IE do not

have clinical stigmata.²⁹ While transesophageal echocardiogram (TEE) has a higher sensitivity compared with TTE for *S. aureus* infective endocarditis, the specificity of both modalities is equivocal. Usage of TEE over TTE is recommended in patients with prosthetic cardiac valves or intracardiac devices. Patients with complicated *S. aureus* bacteremia requiring a prolonged (≥ 6 week) course of anti-staphylococcal therapies need not undergo a TEE so long as a TTE is done to investigate for surgical indications of native IE.⁷

Other imaging modalities, including cardiac magnetic resonance, cardiac CT, positive emission tomography-computed tomography (PET-CT), and CT angiography can complement echocardiography. Foreexample CT angiography can detect abscesses and mycotic aneurysms with diagnostic accuracy similar to that of TEE, in addition to characterizing degree of perivalvular involvement, aortic and coronary vessel anatomy, and aid in preoperative planning.^{27,30}

While there are no recommendations for end-of-therapy echocardiogram performance, we recommend obtaining one in select cases of IE in which relapse risk is significant. Given common persistence of valvular vegetations, repeat TTE can only be used as a new baseline, which can be compared with future TTEs if suspicion for IE relapse is high enough to warrant further investigation.

ASSESSMENT FOR METASTATIC PHENOMENA AND SOURCE CONTROL

Determining source and complications of *S. aureus* bacteremia informs diagnostic and therapeutic interventions. Directed questioning about recent procedures, trauma, or underlying comorbidities may suggest a source of *S. aureus* bacteremia. Similarly, the presence of foreign bodies or acute pain syndromes may identify metastatic *S. aureus* complications.

Management and outcomes differ depending on the source of *S. aureus* bacteremia. The commonest sources of hospital-acquired and community-acquired *S. aureus* bacteremia are line-related and skin/soft tissue infections, respectively.¹⁵ Upwards of 40% of individuals with *S. aureus* bacteremia do not have an apparent source. Pleuropulmonary, osteoarticular, and endovascular sources are also recognized, albeit in lower frequencies.^{15,31} The urinary tract is an uncommon source of *S. aureus* bacteremia and may reflect hematogenous seeding as opposed to urinary infection. One in 5 patients with *S. aureus* bacteremia and concomitant *S. aureus* bacteriuria have vertebral osteomyelitis or psoas abscesses and should be closely assessed for same.³²

Patients with *S. aureus* bacteremia require a meticulous physical examination followed by corresponding investigations, as dissemination to osteoarticular, vertebral, and visceral organs is common. For instance, severe headaches should prompt additional investigations for embolic seeding to the brain from endocarditis, and arthropathies should prompt arthrocentesis for assessment of septic arthritis.

Table 2 Surgical Indications for *Staphylococcus aureus* Endocarditis*

Indication	Classification of Recommendations
Left-sided endocarditis	Strong
Endocarditis induced valve dysfunction resulting in heart failure	Strong
Endocarditis induced heart block, annular or aortic abscess, or destructive penetrative lesions	Strong
Persistent infection (characterized as persistent bacteremia or fever ≥ 5 -7 days after initiation of anti-staphylococcal antibiotics)	Strong
Relapsing prosthetic valve endocarditis despite an appropriate antimicrobial course	Moderate
Recurrent emboli and persistent vegetations despite appropriate antimicrobial therapy	Moderate
Vegetations >10 mm in size with clinical evidence of embolic phenomena despite appropriate antimicrobial therapy	Weak
Right-sided endocarditis with symptomatic severe valve dysfunction AND evidence of persistent infection	Weak

*Adapted from the 2016 American Association for Thoracic Surgery consensus guidelines.³⁷

Examination for vertebral tenderness should always be conducted, as vertebral discitis can present occultly or may be erroneously attributed to mechanical back pain. Palpation of the vertebrae will elicit point tenderness over the disc involved.³³ Accordingly, an MRI of the spine should be considered even if findings on clinical assessment are subtle. Repeat MRI may be considered in select circumstances of suspected acute discitis, as radiographic findings of vertebral discitis may lag behind symptoms for 10 days.³⁴

PET-CT is an increasingly utilized modality in identifying metastatic complications of *S. aureus* bacteremia for intervention, particularly when routine investigations, including echocardiogram, are nondiagnostic despite a high pretest probability (eg, confirming vascular graft infection in an individual with unexplained persistent *S. aureus* bacteremia).³⁵ However, the expense and need for specialized radiotracers may limit the practicality of PET-CT.

White blood cell scans have a role in evaluating embolic phenomenon except for cases with vertebral discitis, as significant uptake of leukocytes within the bone marrow conflicts interpretation.

Achieving source control in patients with *S. aureus* bacteremia hastens clearance of bacteremia and reduces associated mortality.³⁶ Endovascular devices, including central lines and intracardiac devices, should be removed in all cases of *S. aureus* bacteremia, where feasible. Patients with *S. aureus* bacteremia and prosthetic heart valves or vascular

grafts should be investigated for infection. Non-endovascular material, including osteoarticular hardware, typically do not require additional investigations unless directed by clinical examination. Confirmed septic arthritis or epidural abscess require surgical consultation for irrigation and debridement. Similarly, expeditious surgical or radiological drainage are needed in cases with intramuscular or intra-abdominal dissemination. Cardiovascular Surgery consultation is valuable in all cases of *S. aureus* IE (Table 2³⁷).

DURATION OF THERAPY

Repeat BCx are necessary to document bacteria clearance and establish duration of therapy. At minimum, 2 weeks of intravenous anti-staphylococcal therapy from the first negative BCx is needed—and can only be considered when *S. aureus* bacteremia has met a series of criteria to be considered *uncomplicated*. Different criteria have been proposed to define the constituents of an *uncomplicated S. aureus* bacteremia. Based on current literature and our expert opinion, the following should be met to consider *S. aureus* bacteremia as *uncomplicated*: 1) clearance of *S. aureus* bacteremia and corresponding clinical defervescence within the first 48–72 hours of anti-staphylococcal therapy; 2) removable foci of infection; 3) absence of metastatic phenomena; 4) absence of endovascular foreign material (eg, prosthetic valves, cardiac devices, vascular grafts); 5) no evidence of endocarditis on echocardiogram.^{38,39}

S. aureus bacteremia is considered *complicated* when the aforementioned criteria are not met. At minimum, 4 weeks of intravenous anti-staphylococcal therapy from the first negative BCx is needed. Six weeks of therapy is recommended when deep-seated infection, including endocarditis or osteomyelitis, is present (Figure).

INFECTIOUS DISEASES CONSULTATION

ID specialist consultation is recommended in all cases of *S. aureus* bacteremia, given its association with improved outcomes.^{40,41} Benefits of ID consultation have a legacy effect, with improved patient outcomes of at least 5 years.⁴² Reduction of mortality in patients with *S. aureus* bacteremia was more pronounced with bedside ID consultant compared with telephonic consultations.⁴³ The specific mechanisms in which ID consultation improves outcomes remains unclear; rendering it difficult to characterize the benefit of any unique intervention.

CONCLUSION

The significant prevalence of *S. aureus* bacteremia coupled with its high mortality rate behooves clinicians to be well versed in managing this bloodstream infection. Although no 2 cases of *S. aureus* bacteremia are the same, the management of *S. aureus* bacteremia should involve a series of common evidence-informed clinical considerations. Of all considerations, ID consultation remains quintessential and

should be employed for all cases of *S. aureus* bacteremia, regardless of patient characteristics or clinical presentation.

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